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Morita, Hideaki ; Moro, Kazuyo ; Koyasu, Shigeo

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Innate lymphoid cells in allergic and nonallergic inflammation

Hideaki Morita, MD, PhD,[a,b] Kazuyo Moro, PhD,[c,d] and Shigeo Koyasu, PhD[e,f] *Davos, Switzerland, and Yokohama and Tokyo, Japan*

In the last decade, the full picture of the role of innate lymphoid cells (ILCs) has been gradually revealed. ILCs are classified into 3 groups based on their transcription factors and cytokine production patterns, which mirror helper T-cell subsets. Unlike T cells and B cells, ILCs do not have antigen receptors. They promptly respond to multiple tissue-derived factors, such as cytokines and alarmins, and produce multiple proinflammatory and immunoregulatory cytokines. It has been reported that ILC-derived cytokines are important for the induction and regulation of inflammation. Accumulating evidence suggests that ILCs play substantial roles in protection against infection and the pathogenesis of inflammatory diseases, such as allergic diseases and autoimmune diseases. Different ILC subsets localize in distinct tissue/organ niches and receive tissue-derived signals on different types of inflammation, which allows them to acquire diverse phenotypes with specialized effector capacities. In this review we highlight the roles of ILCs in a variety of organs, such as the airway, skin, and gastrointestinal tract, in the context of allergic and nonallergic inflammation. (J Allergy Clin Immunol 2016;138:1253-64.)

Key words: *Innate lymphoid cell, asthma, viral infection, obesity, atopic dermatitis, psoriasis, eosinophilic gastrointestinal disorder, inflammatory bowel disease*

Abbreviations used

AD:	Atopic dermatitis
AHR:	Airway hyperresponsiveness
BALF:	Bronchoalveolar lavage fluid
CD:	Crohn disease
cNK:	Classical natural killer
CRTH2:	Chemoattractant receptor-homologous molecule expressed on T_H2 cells
EGID:	Eosinophilic gastrointestinal disorder
EoE:	Eosinophilic esophagitis
GWAS:	Genome-wide association study
HDM:	House dust mite
IBD:	Inflammatory bowel disease
ILC:	Innate lymphoid cell
ILC1:	Group 1 innate lymphoid cell
ILC2:	Group 2 innate lymphoid cell
ILC3:	Group 3 innate lymphoid cell
KLRG1:	Killer cell lectin-like receptor G1
LTD_4:	Leukotriene D_4
LTi:	Lymphoid tissue inducer
NCR:	Natural cytotoxicity receptor
NK:	Natural killer
OVA:	Ovalbumin
PGD_2:	Prostaglandin D_2
RORγt:	Retinoic acid–related orphan receptor γt
STAT:	Signal transducer and activator of transcription
T-bet:	T-box transcription factor
Treg:	Regulatory T
TSLP:	Thymic stromal lymphopoietin
UC:	Ulcerative colitis
WAT:	White adipose tissue

Innate lymphoid cells (ILCs) are recently identified immune cells that have lymphoid morphology but lack an antigen receptor. Instead of antigen stimulation, ILCs promptly respond to multiple cell-derived factors, such as cytokines and ***eicosanoids***, which are produced by other cells in response to pathogen-associated molecular patterns and ***damage-associated molecular patterns***, leading to their designation as innate immune cells. ILCs develop from common lymphoid progenitors in fetal liver and bone marrow and are dependent on ***common γ chain*** receptor signaling and the transcription factor Id2.[1-3] They have been classified into 3 different subpopulations, namely group 1 innate lymphoid cells (ILC1s), group 2 innate lymphoid cells (ILC2s), and group 3 innate lymphoid cells (ILC3), which resemble T_H cell subsets, according to their distinct patterns of cytokine production and transcription factors (Fig 1).[4]

ILC1s, which resemble T_H1 cells, are defined by production of the type 1 cytokine IFN-γ and expression of ***T-box transcription factor (T-bet)*** and have been implicated in immunity against intracellular pathogens, such as viruses and intracellular

From [a]the Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos; [b]the Christine Kühne-Center for Allergy Research and Education, Davos; [c]the Laboratory for Innate Immune Systems and [e]the Laboratory for Immune Cell Systems, RIKEN Center for Integrative Medical Sciences, Yokohama; [d]the Division of Immunobiology, Department of Medical Life Science, Graduate School of Medical Life Science, Yokohama City University; and [f]the Department of Microbiology and Immunology, Keio University School of Medicine, Tokyo.

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Corresponding author: Shigeo Koyasu, PhD, Laboratory for Immune Cell Systems, RIKEN Center for Integrative Medical Sciences, Yokohama, Japan. E-mail: shigeo.koyasu@riken.jp.

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Terms in boldface and italics are defined in the glossary on page 1254.

bacteria.[3,5,6] Group 1 ILCs include 2 different populations: classical natural killer (cNK) cells and ILC1s. Both cNK cells and ILC1s produce IFN-γ on activation with IL-12, IL-15, and IL-18. The cytotoxic activity of cNK cells is mediated by the production of granzymes and perforin similar to $CD8^+$ cytotoxic T cells,[7] whereas ILC1s do not produce granzymes or perforin. Although cNK cells develop from $Id2^+$ progenitors, which have the potential to develop into all ILC subsets, ILC1s develop from a $PLZF^{high}$ ILC progenitor that has lost the potential to develop into either cNK cells or lymphoid tissue inducer (LTi) cells, a type of ILC3.

ILC2s, which are phenotypically similar to T_H2 cells, are defined by the production of the type 2 cytokines IL-4, IL-5, IL-9, and IL-13 and expression of GATA-3.[8-15] Although GATA-3 has been reported to be indispensable for the development of all IL-7 receptor α^+ ILC subsets (ILC1s, ILC2s, and ILC3s), excluding cNK cells,[16,17] it is a functional requirement for the development of ILC2s. The designation ILC2 collectively refers to natural helper cells and nuocytes (inflammatory ILC2s). Although natural helper cells exist in diverse tissues in the steady state, nuocytes or inflammatory ILC2s are induced in IL-25–mediated inflammation. ILC2s can be activated by various cytokines, such as IL-33, IL-25, ***thymic stromal lymphopoietin (TSLP)***,[8-11] and IL-1β,[18,19] as well as eicosanoids, such as prostaglandin D_2 (PGD_2)[20] and leukotriene D_4 (LTD_4).[21] ILC2s also produce amphiregulin, a member of the epidermal growth factor family, on activation.[22] Therefore ILC2s have been implicated in immunity against helminths, allergic diseases, and tissue repair.

ILC3s, which resemble T_H17 cells, are defined by the production of IL-17A and IL-22 and by expression of retinoic acid–related orphan receptor γt (RORγt) and have been implicated in immunity against extracellular bacteria and autoimmune diseases.[4] ILC3s comprise 3 different populations: LTi cells,[23,24] natural cytotoxicity receptor $(NCR)^+$ ILC3s, and NCR^- ILC3s. LTi cells express CCR6 and produce IL-17A, IL-17F and IL-22 on activation with IL-1β and IL-23. They have heterogeneous expression of CD4 and are a source of lymphotoxin, which is necessary for the formation of secondary lymphoid tissues.[23,24] NCR^+ ILC3s and NCR^- ILC3s are distinguished by the expression of NCRs, such as NKp44 in human subjects and NKp46 in mice. Both cell populations produce IL-22 on activation by IL-1β and IL-23,[4,25-31] but NCR^+ ILC3s are strong producers of IFN-γ.

Interestingly, ILCs display functional plasticity in response to environmental cues, which enables them to respond promptly to environmental changes. For instance, conversion between ILC1s and ILC3s[30] and ILC1s and ILC2s[18,19,32,33] has been reported in human subjects. In brief, ILC3s differentiate into ILC1s on IL-12 stimulation, followed by T-bet induction, whereas ILC1s revert to ILC3s on stimulation with IL-23, IL-1β, and retinoic acid, which are found in the intestine in patients with Crohn disease (CD).[30] In addition, ILC2s differentiate into ILC1s on IL-12 stimulation, followed by T-bet induction, whereas ILC1s revert to ILC2s on stimulation with IL-4, which is found in the lungs in patients with chronic obstructive pulmonary disease and in nasal tissue in patients with chronic rhinosinusitis with nasal polyps.[18,19,32,33] These findings suggest that ILCs might receive specific tissue-derived signals in response to different types of inflammation and subsequently acquire diverse phenotypes with specialized effector capacities.

ILCs IN ALLERGIC AIRWAY INFLAMMATION

A recent genome-wide association study (GWAS) showed that genetic polymorphisms in the gene encoding IL-33, which is a

GLOSSARY

CHITIN: Also known as poly-N-acetyl-D-glucosamine, a polysaccharide found in the cell wall of fungi and the integument of insects and crustaceans. Its structure is similar to cellulose. It is used in the pesticide industry as a fertilizer that deters soil nematode growth. Intra-airway administration of chitin induces asthma-like airway inflammation in mice.

COMMON γ CHAIN: A signal-transducing chain for multiple type I cytokine receptors (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21), also known as CD132. Janus kinase 3 (JAK3) is used for common γ chain signaling. Common γ chain mutations are the cause of X-linked severe combined immunodeficiency (X-SCID). Autosomal recessive mutations in the JAK3 gene result in a similar phenotype as X-SCID.

DAMAGE-ASSOCIATED MOLECULAR PATTERNS (DAMPs): Molecules produced by cell damage caused by infection, toxins, burns, trauma, or hypoperfusion. Alarmins are a specific DAMP produced to enhance the innate immune response to infection. Other examples include heat shock protein and monosodium urate.

EICOSANOIDS: Arachidonic acid–derived compounds that act as inflammatory mediators. Examples include prostaglandins and leukotrienes. The term is based on the Greek word *eikosi*, which means 20 (the number of carbon atoms in arachidonic acid).

IMIQUIMOD: A Toll-like receptor 7 ligand used as a pharmaceutical topical product for the treatment of condyloma acuminata, actinic keratosis, and superficial basal cell carcinoma. Topical application of imiquimod induces psoriasis-like skin inflammation in mice.

LAMINA PROPRIA: A layer of the mucus membrane that lies beneath the epithelium and contains connective tissue, lymphocytes, mast cells, and plasma cells.

PAPAIN: A cysteine protease present in papaya fruit. One of its main uses in the food industry is as a meat-tenderizing agent. Intra-airway administration of papain induces asthma-like airway inflammation in mice.

RECOMBINATION-ACTIVATING GENE *(Rag)*: A lymphoid-specific gene that produces protein critical for V(D)J recombination. Rag stands for recombination-activating gene and includes Rag1 and Rag2 proteins. Rag1 or Rag2 deficiency leads to the deficiency of T, B, and NKT cells and results in severe combined immunodeficiency.

STEROID-RESISTANT ASTHMA: Often defined in the literature as an adult asthmatic patient whose FEV_1 percent predicted does not improve by 10% to 12% after a course of 20 mg of prednisone twice daily for 7 days.

T-box TRANSCRIPTION FACTOR (T-bet): A member of the T-box family of transcription factors that is encoded by the gene *Tbx21* and activated by IFN-γ. Its induction in $CD4^+$ T cells then stimulates additional IFN-γ production, resulting in a positive amplification loop for T_H1 differentiation.

THYMIC STROMAL LYMPHOPOIETIN: A cytokine secreted by gastrointestinal, skin, and lung epithelial cells that promotes a T_H2 differential through its effect on tissue dendritic cells and ILC2s. Its name arises from its initial identification in thymic stromal cells.

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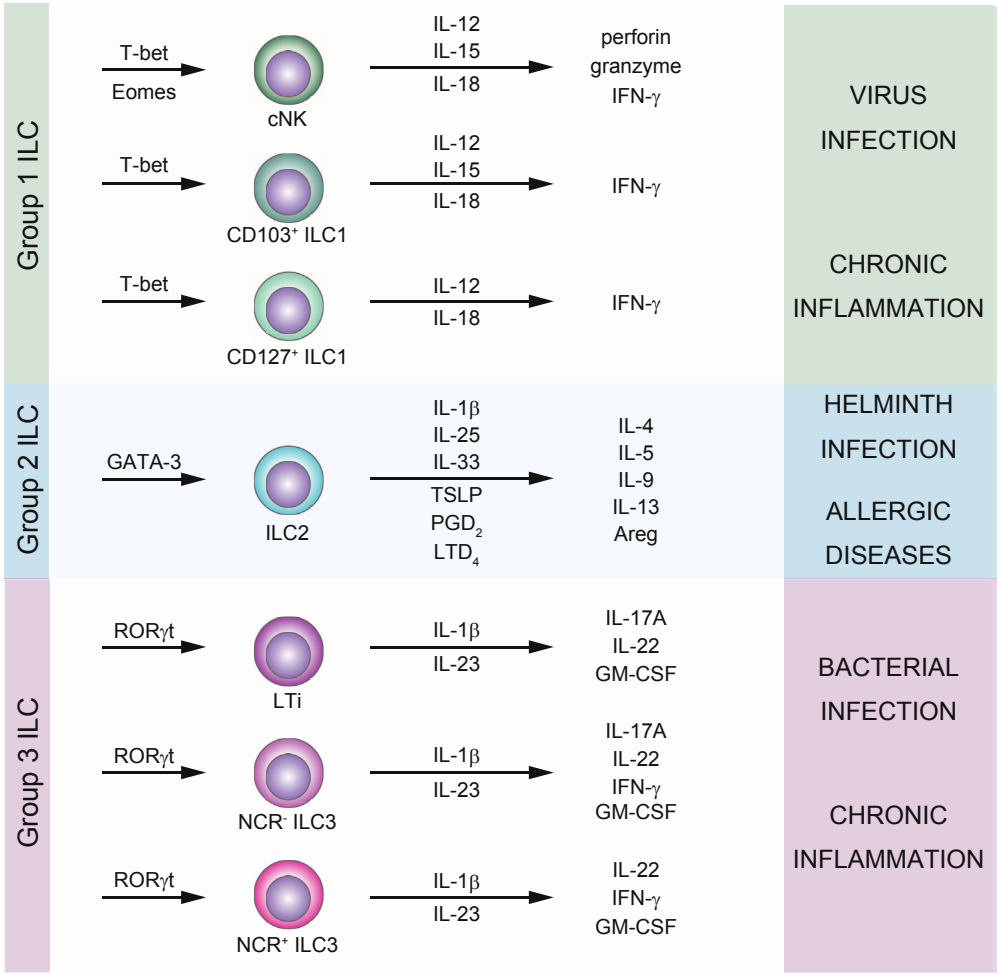

FIG 1. Effector subsets of ILCs. ILCs are divided into 3 different subsets based on their different transcription factors and cytokine expression. ILC1s produce type 1 cytokines, such as IFN-γ, on stimulation with IL-12, IL-15, and IL-18 and express T-bet. These cells are involved in immune responses against intracellular pathogens and act in chronic inflammation. Group 2 ILCs produce type 2 cytokines, such as IL-4, IL-5, IL-9, and IL-13, on stimulation with epithelium-derived cytokines, such as IL-33, IL-25, TSLP, eicosanoids, and IL-1β. These cells are involved in immune responses against helminths or fungi and induce allergic inflammation. ILC3s produce type 3 cytokines, such as IL-17A and IL-22, in response to IL-1β and IL-23 stimulation. These cells play an important role in defense against extracellular pathogens and chronic inflammation. *Areg*, Amphiregulin; *Eomes*, eomesodermin.

major activator of ILC2s, and its receptor IL-1RL1 (ST2) are strongly linked to asthma development.[34,35] Although the genes that encode IL-33 and IL-1RL1 are located on different chromosomes, these 2 genes have consistently been identified in many reports, strongly suggesting that the IL-33–IL-1RL1 pathway and ILC2s are involved in asthma pathogenesis.[36] Indeed, in human subjects a recent study showed that the frequency of ILC2s, as defined by the expression of chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRTH2), IL-7 receptor in peripheral blood[37-39] and bronchoalveolar lavage fluid (BALF),[39-41] and IL-33 levels in BALF,[40] were increased in asthmatic patients compared with control subjects. Moreover, the frequency of ILC2s in peripheral blood[38] and BALF,[40] as well as IL-33 levels in BALF,[40] were negatively correlated with airway function, indicating that ILC2s and IL-33 are involved in asthma pathogenesis.

A recent study showed that ILC2s are involved in eosinophilic asthma–like airway inflammation, including eosinophil infiltration, airway hyperresponsiveness (AHR), and mucus production, even in the absence of acquired immunity, such as T cells, B cells, and IgE antibody.[42-44] In addition, in mice inhalation of epithelium-derived cytokines, such as IL-33 and IL-25, induces eosinophilic asthma–like airway inflammation accompanied by AHR, even in ***recombination-activating gene (Rag)***$^{-/-}$ mice, which lack T cells, B cells, and natural killer (NK) T cells.[42-46] In contrast, IL-33–induced airway inflammation was diminished in *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice, which lack all lymphocytes, including ILCs, but was restored to some extent by engraftment of ILC2s.[42] These findings clearly show that ILC2s induce eosinophilic airway inflammation independent of acquired immunity on activation by epithelium-derived cytokines, such as IL-33 and IL-25 (Fig 2). It has been shown recently that many asthma-related antigens, such as protease allergens, fungal extracts, and viral infection, trigger IL-33 and IL-25 production from epithelial cells and various immune cells and induce eosinophilic asthma–like airway inflammation through activation of lung ILC2s

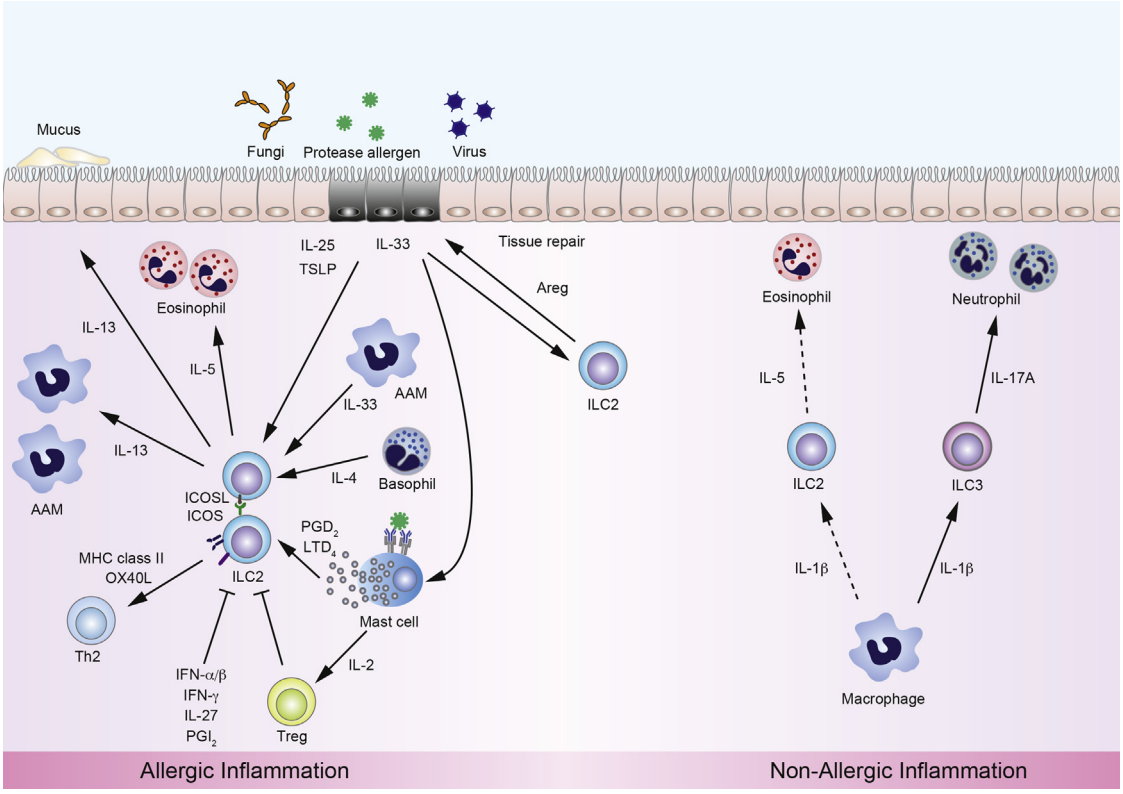

FIG 2. Roles of ILCs in allergic and nonallergic airway inflammation. In patients with allergic airway inflammation, protease allergens, such as HDM, and fungal and viral infection induce IL-33, IL-25, and TSLP from epithelial cells and macrophages. These cytokines induce production of type 2 cytokines, such as IL-5 and IL-13, from ILC2s, which leads to eosinophilic inflammation, even in the absence of acquired immunity. PGD_2 and LTD_4 from mast cells also induce type 2 cytokines from ILC2s, and basophil-derived IL-4 and inducible costimulator *(ICOS)*/ICOS ligand interaction on ILC2s are important for ILC2 activation. IL-5 from ILC2s promotes accumulation of eosinophils, and IL-13 induces goblet cell hyperplasia and accumulation of alveolar macrophages. ILC2s also activate T_H2 cells through OX40 ligand *(OX40L)* and MHC class II. IFN-α/β, IFN-γ, IL-27, prostaglandin I_2 *(PGI_2)*, and Treg cells suppress ILC2 activation and attenuate ILC2-mediated airway inflammation. In patients with nonallergic airway inflammation, such as obesity-associated asthma, IL-1β derived from macrophages induces IL-17A production by ILC3s, which results in induction of neutrophils and AHR. Macrophage-derived IL-1β can also activate ILC2s and enhance airway inflammation. *Areg*, Amphiregulin.

independent of acquired immunity.[42,44,47-49] Furthermore, many allergens, such as house dust mites (HDMs), cockroaches, fungi, and pollens were reported to possess protease activities.[50] Although protease activities of allergens destroy epithelial cells, which enables the allergen to cross the tissue barrier, resulting in allergen sensitization, these protease activities also induce IL-33 release from epithelial cells, which induces asthma-like airway inflammation through ILC2 activation. In fact, ***papain***, which is homologous to the HDM allergen Der 1 and used in the food industry, is known to be a cause of occupational asthma.[51] Administration of papain to mice induces IL-33 secretion from lung epithelial cells and induces eosinophilic asthma–like airway inflammation through activation of lung ILC2s by IL-33.[42,44,47,52] Under these conditions, it was shown that basophil-derived IL-4[53] and inducible costimulator/inducible costimulator ligand interaction on ILC2s[54] play important roles in the activation of lung ILC2s. However, mast cells activated by IL-33 play a protective role by expanding regulatory T (Treg) cells that suppress ILC2 activation (Fig 2).[42,55]

Administration of *Alternaria* species, a major fungal aeroallergen, also induces eosinophilic airway inflammation in mice through activation of lung ILC2s by IL-33 and IL-25.[21,47,48] In agreement with this, it was shown that IL-33 expression was increased in sinonasal epithelial cells from patients with chronic rhinosinusitis with nasal polyps on stimulation with fungal extracts from *Alternaria alternata*, *Aspergillus fumigatus*, and *Cladosporium herbarum*.[56] ***Chitin***, a key structural component of fungi, HDM, and helminths, is also known to induce eosinophilic airway inflammation independent of acquired immunity.[57] Recently, it was shown that ILC2s activated by IL-33, IL-25, and TSLP are essential for the induction of chitin-induced eosinophilic airway inflammation through type 2 cytokine production.[58]

Viral infection also induces asthma-like airway inflammation through activation of ILC2s independent of acquired immunity. For example, it was shown that H3N1 influenza A virus infection induced AHR through activation of lung ILC2s by alveolar macrophage–derived IL-33.[49] In addition, respiratory syncytial virus infection induced AHR and mucus accumulation through activation of lung ILC2s by epithelium-derived TSLP but not IL-33.[59,60] Rhinovirus infection of neonatal mice induced long-term mucus metaplasia and AHR through activation of lung ILC2s by epithelium-derived IL-25.[61] Interestingly, unlike

neonatal mice, IL-25 production from epithelial cells and ILC2 accumulation were not observed in adult mice infected by rhinovirus,[61] suggesting that early-life rhinovirus infection might contribute to the development of asthma later through activation of lung ILC2s, which results in chronic mucus metaplasia and AHR. In support of this notion, a recent epidemiologic study showed that wheezing episodes on viral respiratory tract infections, such as rhinovirus and respiratory syncytial virus in early life, are strongly associated with asthma development.[62] Taken together, activation of ILC2s by IL-33, IL-25, and TSLP induced by allergens and viruses is crucial for initiation of asthma-like airway inflammation development before antigen sensitization.

ILC2s contribute not only to the initiation of innate allergic airway inflammation but also to the enhancement of allergic inflammation by interacting with other immune cells. The role of ILC2s in acquired immunity was analyzed in mouse models that require a sensitization phase before the challenge phase, such as HDM, ovalbumin (OVA), and papain exposure models. In an HDM model and papain exposure model, eosinophilic airway inflammation was attenuated in mice that were lethally irradiated and transplanted with bone marrow cells from *Rora*$^{sg/sg}$ mice. Because *Rora* is critical for ILC2 differentiation, these mice lack ILC2s (ILC2-deficient mice). T-cell responses to antigen were significantly decreased in ILC2-deficient mice compared with control mice.[63,64] ILC2s have been reported to have a direct effect on T_H2 cell activation through OX40 ligand[65] and MHC class II[66] on ILC2s *in vitro*. In addition, ILC2s have also been reported to have an indirect effect on memory T_H2 cell recruitment through induction of CCL17 from dendritic cells.[67] These mechanisms might be involved in the activation of acquired immunity (Fig 2). In contrast, in an OVA model eosinophilic airway inflammation was comparable between ILC2-deficient mice and control mice.[63] Whereas HDM and papain exposure model mice were sensitized by intranasal antigen administration, OVA model mice were sensitized by systemic antigen administration. Therefore it is possible that ILC2s have crucial roles in the initiation of local immune responses to antigen but not in the initiation of systemic immune responses.

In human lungs ILC2s are located in proximity to mast cells,[68] suggesting that ILC2s can also interact with mast cells. CRTH2, a distinctive marker on human ILC2s, is a receptor for PGD_2 that is produced by activated mast cells. It was shown that PGD_2 induces migration of human ILC2s through CRTH2[20,69] and induces type 2 cytokine production from human ILC2s.[20,68] Another lipid mediator, LTD_4, derived from mast cells was also shown to activate ILC2s in mice. LTD_4 induces type 2 cytokine production from mouse ILC2s and accumulation of lung ILC2s in *Alternaria* species–induced eosinophilic inflammation.[21] PGD_2 and LTD_4 are released by mast cells on degranulation induced by IgE cross-linking.[70,71] Therefore these findings suggest that mast cells activated on IgE cross-linking contributes to enhancement of allergic airway inflammation through recruitment and activation of ILC2s. In contrast, IL-33 induces IL-2 production from mast cells that promotes Treg cell expansion[42] but not degranulation of mast cells.[72,73] Therefore mast cells activated by IL-33 contribute to the regulation of allergic airway inflammation through suppression of ILC2s by Treg cells (Fig 2).

Recent studies suggest that ILC2s also have important roles in steroid-resistant severe allergic airway inflammation and persistence of chronic airway inflammation.[39,43] In human subjects it was shown that the number of total ILC2s and type 2 cytokine–producing ILC2s in peripheral blood and sputum were significantly increased in patients with systemic steroid-dependent severe eosinophilic asthma compared with those with mild asthma. In contrast, the number of type 2 cytokine–producing $CD4^+$ T cells did not differ significantly between these 2 patient groups.[39] These findings suggest that ILC2s, but not $CD4^+$ T cells, play a significant role in ***steroid-resistant asthma*** and promote the development of airway inflammation in patients with systemic steroid-dependent severe eosinophilic asthma. Likewise, corticosteroids suppressed T_H2 cells, but not ILC2s, in an OVA-induced asthma model when a low dose of IL-33 was coadministered with OVA, which results in corticosteroid-resistant airway inflammation. In this model TSLP was shown to be a key molecule that induces corticosteroid resistance of ILC2s by controlling phosphorylation of signal transducer and activator of transcription (STAT) 5 and expression of Bcl-xL. Furthermore, STAT5 inhibitors abrogated steroid resistance in this model.[43]

It is known that symptoms persist in most patients with occupational asthma, even years after removal of exposure to the occupational antigen.[74] However, little is known about the mechanisms regulating these persistent symptoms. It was recently shown that ILC2s, but not T cells, play a pivotal role in the persistence of asthma. Three allergens (ie, HDM, ragweed, and *Aspergillus* species) induced persistent allergic inflammation in mice, which exhibited persistent inflammation and AHR for more than 6 months after cessation of allergen exposure. In these models depletion of T cells reduced sustained airway inflammation to some extent but did not eliminate sustained AHR. In contrast, depletion of ILC2s completely eliminated sustained airway inflammation and AHR, indicating the importance of ILC2s in the persistence of chronic asthma.[40]

Taken together, ILC2s play a pivotal role in the initiation, enhancement, and steroid resistance of allergic airway inflammation. Consequently, regulation of ILC2 activation is likely an important target to control asthma. Recently, IFN-α/β,[75,76] IFN-γ,[75-77] IL-27,[75,76,78] Treg cells,[42] and prostaglandin I_2,[79] were shown to suppress ILC2 activation *in vitro* and *in vivo* (Fig 2). These findings open a new window for the prevention and treatment of asthma.

ILCs IN NONALLERGIC AIRWAY INFLAMMATION

Although asthma has been considered a single disease for years, recent studies indicate that asthma is actually a heterogeneous disease composed of different phenotypes, such as allergic asthma, including early-onset allergic asthma and late-onset persistent eosinophilic asthma, and nonallergic asthma, including neutrophilic asthma and obesity-related asthma.[80] As mentioned before, evidence has accumulated that ILC2s are involved in allergic-type asthma. However, the role of ILCs in nonallergic asthma remains unclear. Obesity has been suggested to play a substantial role in the development of asthma.[81] Recent findings suggest that ILCs are also involved in obesity-associated allergic airway inflammation. The numbers of ILC3s in the lungs of high-fat diet–fed obese mice was increased compared with those in standard diet–fed mice. In addition, AHR was induced in high-fat diet–fed obese mice in the absence of an antigen challenge. This obesity-induced AHR is independent of acquired immunity but dependent on IL-17A. Obesity-induced AHR was ameliorated in *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice, which lack all ILCs in addition to T cells, B cells, and NKT cells, and adoptive transfer of ILC3s

to *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice restored obese-induce AHR, suggesting that IL-17A–producing ILC3s play a critical role in obesity-induced AHR. Under these conditions, IL-1β produced by macrophages on activation of the nucleotide-binding domain, leucine-rich repeat/pyrin domain-containing 3 pathway induces IL-17A production from ILC3s (Fig 2).[82]

It has recently been shown that obesity contributes to airway inflammation not only through activation of ILC3s but also through ILC2 activation. ILC2 numbers in the lungs of high-fat diet–fed obese mice were also increased compared with those in low-fat diet–fed mice without antigen challenge. On HDM administration, airway inflammation and AHR accompanied by accumulation of ILC2s and ILC3s were exacerbated in high-fat diet–fed obese mice compared with mice fed a standard diet, suggesting that activation of both ILC2s and ILC3s plays an important role in obesity-associated airway inflammation on HDM challenge.[83] Although the mechanisms for ILC2 activation in high-fat diet–fed obese mice have not been clarified, a recent study showed that IL-1β also activates ILC2s to produce type 2 cytokines,[18,19] suggesting that IL-1β signaling is a possible mechanism underlying obesity-induced ILC2 activation (Fig 2).

Interestingly, unlike in the lungs, it was shown that ILC2 responses in white adipose tissue (WAT) were dysregulated in obese patients. Because the IL-33/ILC2 axis regulates metabolic homeostasis by eliciting beiging of WAT, dysregulation of ILC2s in WAT might be one possible mechanism of obesity.[84] However, the mechanisms that induce dysregulation of ILC2 responses in WAT remain unclear.

Of note, ILC2s promote beneficial tissue repair responses in the lung after acute epithelial damage, such as viral infection. It has been reported that depletion of ILC2s during H1N1 influenza infection impaired lung function and epithelial integrity, which were restored after adoptive transfer of lung ILC2s or administration of amphiregulin, suggesting that ILC2s contribute to lung tissue repair through amphiregulin production (Fig 2).[22] However, as mentioned before, by using a different H3N1 influenza virus, another article showed that ILC2s could be pathogenic during influenza virus infection through IL-13 production.[49] These findings suggest that the roles of ILC2s in the lungs during viral respiratory tract infection might be different depending on the level of tissue damage, types of virus, and environmental factors. Further studies are needed to fully characterize the different roles of ILC2s in the lungs during viral respiratory tract infection.

ILCs IN ALLERGIC SKIN INFLAMMATION

Atopic dermatitis (AD) is the most common chronic and relapsing inflammatory skin disease characterized by type 2–skewed inflammation and epithelial barrier dysfunction.[85] Expression of TSLP,[86] IL-25,[87] and IL-33,[88] which activate ILC2s, was upregulated in lesional skin from patients with AD compared with healthy skin, suggesting that ILC2s play a crucial role in the pathogenesis of AD through activation by these cytokines. Indeed, it has been shown that ILC2s are resident in healthy skin tissue in both human subjects and mice,[89,90] and the frequency of ILC2s was higher in skin tissue from lesional skin of human patients with AD compared with that in healthy subjects.[89,90] The responsiveness of skin ILC2s to epithelium-derived cytokines is still controversial. Salimi et al[90] reported that ILC2s isolated from healthy skin produced type 2 cytokines on stimulation by IL-33 but not IL-25 and TSLP. Conversely, Teunissen et al[91] reported that ILC2s from healthy skin samples produced type 2 cytokines on TSLP, but not IL-33 and IL-25, stimulation. However, IL-17RB (IL-25 receptor), ST2 (IL-33 receptor), TSLP receptor, and CRTH2 were highly upregulated on ILC2s from human AD skin lesions compared with ILC2s from healthy skin,[90] suggesting that ILC2s in AD skin lesions are highly activated and more responsive to stimuli, such as IL-25, IL-33, TSLP, and PGD_2 (Fig 3). The role of ILC2s in allergic skin inflammation has also been investigated by using different mouse models. Overexpression of IL-33[92] and TSLP[93,94] in the skin spontaneously induces AD-like skin inflammation accompanied by itching, eosinophil infiltration, and thickening of the epidermis. In particular, numbers of $Lin^{-}ST2^{+}Sca\text{-}1^{+}$ skin ILC2s were increased in lesional skin from transgenic mice with skin-specific expression of IL-33, indicating involvement of the IL-33–ILC2 axis in this model.[92] Topical treatment with a vitamin D analog, calcipotriol, was also shown to induce AD-like skin inflammation accompanied by eosinophil infiltration, epidermal hyperplasia, and increased type 2 cytokine production.[89] Similarly, a vitamin D analog also induced AD-like skin inflammation in *Rag1*$^{-/-}$ mice, which lack acquired immunity, but depletion of ILCs by an anti-CD25 antibody attenuated skin inflammation, suggesting that ILCs, but not T cells, B cells, and NKT cells, are critical in this model.[89] It is unknown whether similar mechanisms mediate skin inflammation in the above-mentioned mouse models.

Furthermore, the involvement of epithelium-derived cytokines, such as IL-33 and TSLP, in these models is controversial. Kim et al[89] demonstrated that skin inflammation was attenuated in *Tslpr*$^{-/-}$ mice, but not in *Il33*$^{-/-}$ mice, compared with wild-type mice on a C57BL/6 background. In contrast, Salimi et al[90] demonstrated that skin inflammation was attenuated in *Il17rb*$^{-/-}$ mice and *St2*$^{-/-}$ mice, but not *Tslpr*$^{-/-}$ mice, on a BALB/c background. These differences might be due to differences in genetic backgrounds and environmental factors, including microbiota.

Interactions of ILC2s with other cell types have also been shown to be critical in the pathogenesis of allergic skin inflammation. Basophils, which are usually undetectable in healthy control skin, were enriched in the dermis of human AD lesions in close proximity to ILC2s,[95] suggesting that the interaction between ILC2s and basophils is involved in the pathogenesis of AD. Indeed, depletion of basophils attenuated vitamin D analog–induced AD-like skin inflammation in mice. Moreover, conditional depletion of IL-4 in basophils also attenuated vitamin D analog–induced AD-like skin inflammation and accumulation of ILC2s in the skin.[95] Therefore it is likely that basophils play a critical role in the initiation of allergic skin inflammation through activation of skin ILC2s by means of production of IL-4 (Fig 3). Mast cells also accumulated in the lesional skin in human and mouse AD models,[96] suggesting that the interaction between mast cells and ILC2s is also involved in the pathogenesis of AD. Indeed, it has been shown that PGD_2 promotes the migration of skin ILC2s and induces type 2 cytokine production from skin ILC2s. Moreover, the supernatant of IgE/anti-IgE–activated mast cells also induces migration and cytokine production by human skin ILC2s.[20] Because mast cells produce PGD_2 by means of activation through FcεRI, they likely play a role in migration and cytokine production by ILC2s through the effects of PGD_2 (Fig 3). Killer cell lectin–like receptor G1 (KLRG1), which is known

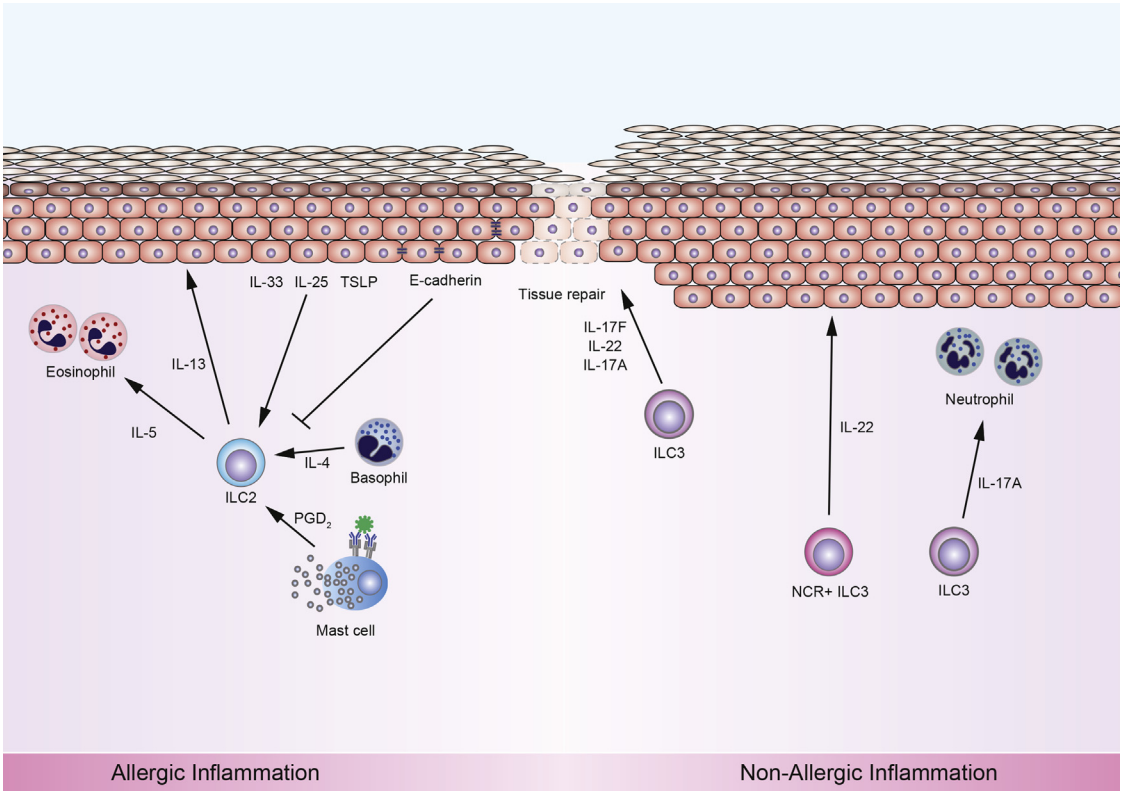

FIG 3. Role of ILCs in allergic and nonallergic skin inflammation. In patients with allergic skin inflammation, such as AD, epithelial cell–derived cytokines, such as IL-33, IL-25, and TSLP, induce type 2 cytokine production from ILC2s. ILC2s from AD lesional skin express IL-17RB (IL-25 receptor), ST2 (IL-33 receptor), TSLP receptor, and CRTH2. Basophils and mast cells accumulate in the lesional skin of patients with AD. Similar to what is observed in patients with allergic airway inflammation, basophil-derived IL-4 is important for ILC2 activation. Mast cell–derived PGD_2 induces type 2 cytokine production from ILC2s. E-cadherin expressed on keratinocytes and Langerhans cells suppresses ILC2 activation by means of ligation to KLRG1 on ILC2s. Decreased expression of E-cadherin in keratinocytes from patients with AD results in persistent activation of ILC2s. In patients with nonallergic skin inflammation, such as psoriasis, IL-22 from NCR^+ ILC3s induces skin thickening, and IL-17A from ILC3s induces neutrophil infiltration. ILC3s accumulate in wound sites through Notch1 and contribute to wound healing through IL-17F, IL-17A, and IL-22.

as an inhibitory receptor on NK cells, is also a known marker of ILC2s in mice.[97] KLRG1 binds to the cell adhesion molecule E-cadherin, which is expressed on keratinocytes and Langerhans cells.[98] KLRG1 was highly expressed on skin ILC2s from patients with AD compared with skin ILC2s from healthy control subjects, and TSLP and IL-33, but not IL-25, upregulated KLRG1 expression on cultured ILC2s. In addition, E-cadherin ligation to KLRG1 on ILC2s suppressed cytokine production from skin ILC2s,[90] suggesting that the KLRG1–E-cadherin interaction plays an important role in the negative feedback mechanisms in activated skin ILC2s (Fig 3). Interestingly, E-cadherin expression was decreased in keratinocytes from AD lesional skin compared with that seen in normal skin.[99] In addition, E-cadherin was downregulated in keratinocytes on short hairpin RNA knockdown of the filaggrin gene that has crucial roles in skin barrier function.[90] These findings suggest that low E-cadherin expression on keratinocytes in patients with AD leads to persistent activation of ILC2s in AD skin lesions.

Taken together, ILC2s are likely involved in the induction of allergic skin inflammation through activation by epithelium-derived cytokines, such as IL-33, IL-25, and TSLP, and interaction with other immune cells.

ILCs IN NONALLERGIC SKIN INFLAMMATION

Psoriasis is a common chronic skin inflammatory disease characterized by epidermal thickness and scaly plaques that affects approximately 2% of the population.[100] Previously, T cells and dendritic cells were considered to play key roles in the pathogenesis of psoriasis through production of cytokines, such as IL-17A, IL-17F, and IL-22. In brief, IL-17A and IL-17F contribute to disease pathogenesis by inducing neutrophilic inflammation, and IL-22 contributes to epidermal hyperplasia (Fig 3).[101] However, recent studies have shown that ILCs, particularly ILC3s that produce IL-17A and IL-22, also play substantial roles in the pathogenesis of psoriasis. The frequency of NCR^+ ILC3s, but not ILC1s or ILC2s, was increased in peripheral blood from patients with psoriasis compared with healthy control subjects.[91,102] Moreover, the frequency of NCR^+ ILC3s was increased in lesional[91] and nonlesional[103] skin from patients with psoriasis compared with healthy skin. Importantly, the frequency of NCR^+ ILC3s in the skin correlated with disease severity determined by the Psoriasis Area and Severity Index.[91] In addition, the frequency of NCR^+ ILC3s in peripheral blood was decreased on anti-TNF antibody treatment and was closely associated with the reduction of disease severity determined by using the Psoriasis

Area and Severity Index.[102] ILC3s from lesional skin of patients with psoriasis can produce IL-22 and, to a lesser extent, IL-17A,[91,102] suggesting that ILC3s have a pathogenic role in psoriasis through IL-22 and, to a lesser extent, IL-17A production.

In mice topical application of ***imiquimod*** induces skin inflammation accompanied by acanthosis and plaque formation that largely resembles the disease phenotype of human psoriasis. In this model γδ T cells and ILC3s, but not T_H17 cells, were the main source of these cytokines. Indeed, imiquimod-induced skin inflammation was induced in *Rag1*$^{-/-}$ mice, which lack acquired immunity, but was completely diminished in *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice, which lack ILCs, and *Rorgt*$^{-/-}$ mice, which lack T_H17 cells and ILC3s.[104] Taken together, these findings suggest that ILC3s have critical roles as effector cells in the development of psoriasis-like skin inflammation in mice through production of IL-17A, IL-17F, and IL-22 (Fig 3).

ILC3s have also been shown to play a substantial role in skin repair. It was shown that RORγt$^+$ ILC3s were recruited to wound sites through epidermal Notch1 signaling in mice. Similarly RORγt$^+$ ILC3s infiltrated human skin after wounding by using a punch biopsy. In addition, wound healing was delayed in mice deficient for RORγt$^+$ ILC3s accompanied by delayed epidermal proliferation and macrophage recruitment.[105] Interestingly, the majority of mouse ILC3s that accumulated in the wound site expressed IL-17F but lower amounts of IL-17A and IL-22. Likewise, human ILC3s accumulating in the wound site expressed IL-17F and IL-17A.[105] These findings suggest that ILC3s contribute to repair of skin tissue through production of IL-17F and, to a lesser extent, IL-17A and IL-22 (Fig 3).

ILCs IN ALLERGIC GASTROINTESTINAL INFLAMMATION

Primary eosinophilic gastrointestinal disorders (EGIDs), including eosinophilic esophagitis (EoE), eosinophilic gastritis, eosinophilic gastroenteritis, and eosinophilic colitis, are disorders that exhibit eosinophil-rich inflammation in the gastrointestinal tract in the absence of known causes for eosinophilia such as parasite infection and drug reaction.[106,107] Although food-specific IgE antibodies were detected in the serum of patients with EGIDs, typical symptoms observed in patients with IgE-dependent food allergy, such as anaphylaxis, were not induced in patients with EGIDs. Therefore EGIDs were considered to be independent of IgE antibodies but dependent on IL-5$^+$IL-13$^+$ T_H2 cell activation by antigens.[106] However, recent findings suggest the involvement of ILC2s in the pathogenesis of EGIDs.

EoE is a chronic, antigen-mediated disease characterized by eosinophil infiltration, esophageal remodeling, subepithelial fibrosis, and smooth muscle dysmotility. Although type 2 cytokines, such as IL-5 and IL-13, were shown to be involved in its pathogenesis,[108,109] the cellular sources of these cytokines were not well clarified. Results from GWASs suggest that the *TSLP* gene is associated with EoE.[110] Indeed, TSLP expression was increased in esophageal biopsy specimens from patients with active EoE compared with control subjects.[110,111] In addition, expression of IL-33 and IL-25 was increased in the esophagus, and the frequency of ILC2s was increased in esophageal biopsy specimens from patients with active EoE compared with those with inactive EoE and control subjects. Importantly, the frequency of ILC2s correlated with the number of eosinophils in esophageal biopsy samples from patients with EoE.[112] These findings strongly suggest that ILC2s have a pathogenic role in patients with EoE through type 2 cytokine production induced by TSLP, IL-33, and IL-25 (Fig 4).

The involvement of ILCs in patients with other types of EGIDs remains unclear. However, it was shown that TSLP and IL-33 expression in sigmoid colon biopsy specimens was increased in patients with eosinophilic gastroenteritis,[113] suggesting that ILC2s are also involved in other types of EGIDs.

ILCs IN NONALLERGIC GASTROINTESTINAL INFLAMMATION

Inflammatory bowel diseases (IBDs), such as CD and ulcerative colitis (UC), are a group of chronic disorders of the gastrointestinal tract characterized by intestinal inflammation and epithelial injury.[114] GWASs have identified several IBD susceptibility loci that contain genes encoding cytokines and cytokine receptor signaling. These loci contain genes related to type 1 immune responses, such as those encoding IFN-γ and IL-12 receptor and its intracellular signaling components, such as STAT1 and STAT4, as well as genes related to type 3 immune responses, such as those encoding IL-23 receptor and its intracellular signaling components, such as STAT3.[115] These findings suggest that type 1 and type 3 cytokines are involved in the pathogenesis of IBD. Indeed, various studies showed that production of the type 1 cytokine IFN-γ by ***lamina propria*** T_H1 cells was increased in patients with CD compared with healthy control subjects but not in patients with UC.[116,117] In addition, production of type 3 cytokines, such as IL-17A and IL-17F, by lamina propria T_H17 cells was increased in patients with CD, as well as in patients with UC.[117,118] ILCs also produce type 1 and type 3 cytokines similar to T cells, but their involvement in IBD *in vivo* is largely unknown.

The frequency of ILC1s in noninflamed intestine was reported to be approximately 10% of total ILCs but increased to 40% in inflamed intestines of patients with CD.[5,30] In human subjects it was shown that there are 2 distinctive subtypes of ILC1s, namely CD127$^+$ ILC1s located in the lamina propria[5,30] and CD103$^+$CD127$^-$ ILC1s located in the epithelium.[6] Both populations produce IFN-γ on IL-12 stimulation in synergy with IL-15 and IL-18. Whereas the frequencies of CD127$^+$ ILC1s and CD103$^+$CD127$^-$ ILC1s were comparable in noninflamed intestinal tissue, the frequency of CD127$^+$ ILC1s, but not CD103$^+$CD127$^-$ ILC1s, was significantly increased in inflamed intestinal tissues from patients with CD.[30] These findings suggest that ILC1s play a role in the pathogenesis of CD through IFN-γ production (Fig 4).

ILC2s were also detected in intestinal tissue from patients with CD. Interestingly, unlike ILC2s in peripheral blood, ILC2s in intestinal tissue from patients with CD produce IFN-γ in addition to IL-13.[32] These findings suggest that ILC2s in intestinal tissue from patients with CD might have received environmental cues, which enable them to convert to ILC1s.

ILC3s comprise the majority of ILCs (NCR$^+$ ILC3s, 70%; NCR$^-$ ILC3s, 15%) in noninflamed human intestine.[5,30] Although the frequency of NCR$^-$ ILC3s in inflamed intestine from patients with CD was comparable with that in noninflamed control intestinal tissue, the frequency of NCR$^+$ ILC3s was dramatically (70% → 20%) decreased in inflamed intestine from patients with CD.[5,119] Intestinal NCR$^+$ ILC3s produce IL-22 in response to IL-23 in synergy with IL-1β.[5,120] In addition, intestinal CD14$^+$ macrophages promote IL-22 production from NCR$^+$ ILC3s through IL-23 and direct interaction (Fig 4).[31]

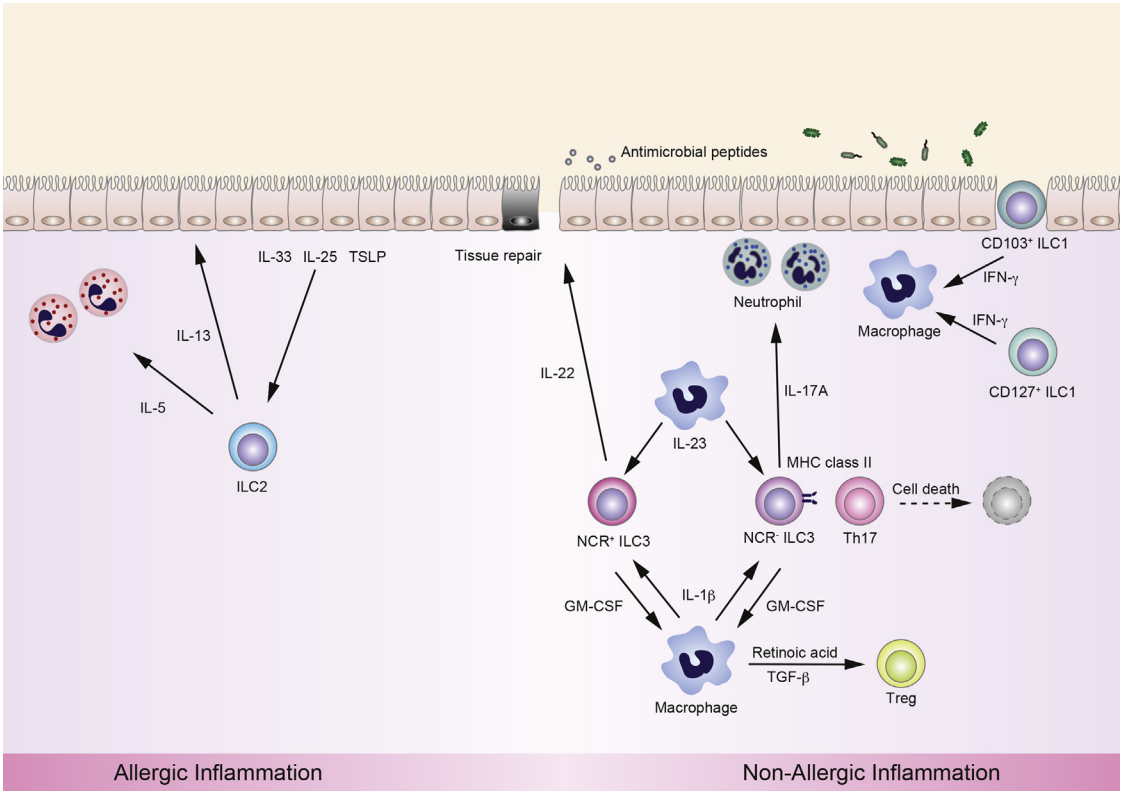

FIG 4. Roles of ILCs in allergic and nonallergic gastrointestinal inflammation. In patients with allergic gastrointestinal inflammation, such as EoE, epithelium-derived cytokines, such as IL-33, IL-25, and TSLP, induce type 2 cytokine production from ILC2s and induce eosinophil infiltration. In patients with nonallergic gastrointestinal inflammation, such as IBD, ILC1s contribute to disease pathogenesis through IFN-γ production. Macrophage-derived IL-23 induces IL-22 production from NCR^+ ILC3s, which is important for intestinal barrier function, wound healing, and antimicrobial production. Decreased frequency of NCR^+ ILC3s might unfavorably affect the pathogenesis of CD. NCR^- ILC3s produce IL-17A together with IL-22. However, the role of IL-17A in human IBD is not clear. ILC3s also have protective roles in the intestine. ILC3s induce cell death in T_H17 cells through MHC class II. In addition, ILC3s produce GM-CSF, which activates macrophages to generate Treg cells by retinoic acid and TGF-β.

The receptor for IL-22 is mainly expressed on tissue cells, such as epithelial cells, and IL-22 mediates intestinal epithelial barrier maintenance and wound healing[31,121,122] and provides functional barrier support by inducing antimicrobials, such as Reg family molecules and S110 proteins.[123] These findings suggest that IL-22 is important for protection against the bacterial infection and tissue injury that occur in patients with IBD. Indeed, in mice ILC3s were an essential source of IL-22 that protected against dextran sodium sulfate–induced colitis, in which the epithelial barrier was disrupted.[124,125] Thus NCR^+ ILC3s might play a protective role in the pathogenesis of IBD through IL-22 production in humans, and the decrease of IL-22–producing NCR^+ ILC3s is unfavorable for patients with IBD (Fig 4). Intriguingly, however, IL-22 was also pathogenic in certain mouse models that mimic human IBD.[126] Further investigation is needed to clarify the roles of IL-22–producing NCR^+ ILC3s in patients with IBD.

Another subset of ILC3s, NCR^- ILC3s, have also been described in the human intestine. Human intestinal NCR^- ILC3s from patients with CD produce IL-17A and IL-17F and, to a lesser extent, IL-22 on IL-23 stimulation.[5,127] However, the role of NCR^- ILC3s in patients with IBD remains unclear. In mice IL-17A–producing NCR^- ILC3s were indispensable for the pathogenesis of mouse colitis models that resemble human IBD, such as *Helicobacter hepaticus*–induced colitis[128] and microbiota-dependent colitis in $Tbx21^{-/-}Rag2^{-/-}$ mice, which lack T-bet in the innate immune system.[129] Anti–IL-17A treatment attenuated intestinal inflammation in these models, suggesting the importance of IL-17A–producing NCR^- ILC3s in the induction of inflammation in these mice. In contrast to mouse models, the frequency of NCR^- ILC3s in inflamed tissues from patients with CD was comparable with that in noninflamed control tissue.[30] In addition, inhibition of IL-17A by the anti–IL-17A antibody secukinumab was ineffective in a clinical trial of patients with moderate-to-severe CD.[130] These findings suggest that NCR^- ILC3s and IL-17A likely do not play a critical role in human CD.

ILC3s were also shown to have a regulatory role in the intestine through interaction with other immune cell subsets, such as macrophages and T cells. It was shown that on IL-1β stimulation, ILC3-derived GM-CSF drives retinoic acid and TGF-β production from macrophages to generate Treg cells that limit intestinal inflammation (Fig 4).[131] MHC class II is expressed on NCR^- ILC3s in both human subjects and mice. MHC class II^+ NCR^- ILC3s suppress the response of $CD4^+$ T cells to commensal bacteria by inducing cell death. Moreover, depletion of MHC class II^+ ILC3s in mice results in commensal

bacteria–dependent colitis induced by increased $CD4^+$ T-cell activation.[132,133] These findings suggest that MHC class II^+ NCR^- ILC3s are important for the maintenance of intestinal homeostasis by limiting bacteria-induced T-cell activation through MHC class II (Fig 4). Interestingly, the expression level of MHC class II on intestinal ILC3s from patients with pediatric CD was significantly lower than that on ILC3s in the intestines of control subjects. In addition, the expression level of MHC class II on ILC3s in the intestines of patients with pediatric CD negatively correlated with the frequency of T_H17 cells.[133] These findings suggest that alteration of MHC class II expression on ILC3s is one of the mechanisms that controls the frequency of pathogenic T_H17 cells.

Taken together, NCR^- ILC3s can have both protective and pathogenic roles in patients with IBD, and further studies are needed to clarify these roles.

CONCLUDING REMARKS

Before the discovery of ILCs, T cells were considered the main cell type responsible for the pathogenesis of inflammatory disease. However, recent studies have shown that ILCs are also essential players in many inflammatory diseases. It is now clear that ILCs play critical roles not only in the initiation of inflammation but also in chronic inflammation and resolution of inflammation through interactions with tissue cells and other immune cells. Further studies are needed to reveal the entire picture of interaction between various cell types and clarify the roles of ILCs in different types of inflammation. Findings from these studies could potentially lead to the development of new therapies for inflammatory diseases that target ILC activation pathways.

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